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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,551	11/27/2001	Jian-Dong Li	HOUSEEI.001A	7280

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,551	LI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-10-03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8-14-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office action is in response to the communication filed 11-10-03.

Claims 1-22 are pending in the instant application.

Election/Restrictions

Applicant's election of Group I in Paper No. 11-10-03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11-10-03. Claims 1-4, 21 and 22 have been examined on their merits as they pertain to Applicants' election of a method of treating mucin overproduction in a mammal comprising the administration of pyridinyl imidazoles, as set forth below.

Claims 1-3 link(s) inventions I, II, III, IV and V. The restriction requirement made which distinguishes between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1-3. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking

claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of p38 MAP kinase following administration of pyridinylimidazole compounds, whereby Nontypeable Hemophilus influenzae (NTHi) cytoplasmic protein induction of mucin (MUC5AC) transcription is inhibited, does not reasonably provide enablement for the treatment of mucin overproduction in any mammal comprising the administration of a pyridimylimidazol inhibitor of p38 MAP kinase to any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating mucin overproduction in any mammal comprising the administration of the pyridimylimidazol inhibitors of p38 MAP kinase, SB203580, SB202190, SB220025, SC68376 or SKF-86002.

The state of the prior art and the predictability or unpredictability of the art. The prior art teaches the specific targeting of pyridinylimidazole compounds in blocking production of IL1-beta and TNF-alpha by monocytes stimulated by LPS in vitro, whereby 2,4,5-triarylimidazole selectively and potently blocks p38 MAP kinase, but not JNK3 or ERK2 (see Su et al, USPN 6,162,613 at col. 2-3; see also Hawkins et al, USPN 5,846,778 at col. 2). The art, however, is silent with respect to the in vivo administration, targeting and subsequent inhibition of p38 MAP kinase by pyrimidylimidazol compounds, as well as with respect to the in vivo treatment of overproduction of mucin using pyrimidylimidazol inhibitors of p38 MAP kinase.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The instant specification teaches a major role for heat stable NTHi cytoplasmic proteins in NTHi-induced MUC5AC transcription in vitro, whereby p38 MAP kinase is phosphorylated and activated. The instant specification teaches the marked induction of MUC5AC by PI3-kinase specific inhibitors LY294002 and wortmannin in vitro (e.g. see page 24 and figure 6 of the instant disclosure). Applicants conclude from their in vitro studies using the p38 MAP kinase specific inhibitors (e.g. the pyridinylimidazole compounds), and using PI3-kinase specific inhibitors (e.g. LY294002 and wortmannin) that wortmannin increased phosphorylation of p38 MAP kinase induction by NTHi, but activation of PI3-kinase-Akt

led to down regulation of p38 MAP kinase phosphorylation induction by NTHi. PI3-kinase-Akt inhibited NTHI-induced MUC5AC transcription by cross-talk with p38 MAP kinase. Therefore, the instant specification teaches that inhibitors of PI3-kinase-Akt signaling by Wortmannin enhances NTHi-induced activation of p38 MAP kinase, and activation by PI3-kinase-Akt attenuates NTHi-induced activation of p38 MAP kinase. These in vitro studies, therefore, suggest that activation of p38 MAP kinase is required for up regulation of MUC5AC by NTHi cytoplasmic proteins.

Applicants, however, have not provided guidance in the specification toward a method of treating mucin overproduction in any mammal comprising the administration of any p38 MAP kinase inhibitor. Applicants have not provided guidance in the specification toward a method of inhibiting p38 MAP kinase in vivo in any mammal following the administration of pyridinylimidazole compounds (e.g. SB203580, SB202190, SB220025...). One skilled in the art would not accept on its face the examples given in the specification and in the prior art - of the increase of MUC5AC transcription following p38 MAP kinase phosphorylation by NTHi cytoplasmic proteins, the marked induction of MUC5AC by PI3-kinase specific inhibitors LY294002 and wortmannin in vitro, nor the p38 MAP kinase specific inhibition in vitro by pyridinylimidazole compounds - as being correlative or representative of the treatment of mucin overproduction in any mammal comprising the inhibition of p38 MAP kinase, in view of the lack of guidance in the specification and known unpredictability associated with the administration and in vivo delivery of pyridimylimidazol inhibitors of p38 MAP kinase. The specification as filed fails to provide any particular guidance which resolves

the unpredictability in the art associated with in vivo delivery and treatment effects provided by the administration of such compounds.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to a method of treating mucin overproduction in any mammal comprising the administration of the pyridimylimidazol inhibitors of p38 MAP kinase, SB203580, SB202190, SB220025, SC68376 or SKF-86002. In order to be fully enabled, it would require undue trial and error and undue experimentation beyond which is taught in the specification to practice the invention drawn to any route of administration of the claimed pyridimylimidazol inhibitors p38 MAP kinase in a mammal such that mucin overproduction is inhibited, and treatment effects are provided for the various conditions associated with mucin overproduction, including otitis media infection, chronic obstructive pulmonary disease, or a chronic sinusitis infection, in turn caused by nontypeable Haemophilu influenzai. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cell and /or tissues harboring p38 MAP kinase, its upstream or downstream effectors, such that the expression of the appropriate mucins is sufficiently inhibited in vivo, and further whereby treatment effects for mucin overproduction are provided in any mammal. Since the specification fails to provide any particular guidance for the successful delivery of any pyridimylimidazol inhibitor of p38 MAP kinase in any organism, and further whereby overproduction of mucins is inhibited and treatment effects provided to an organism, and since determination of these factors

is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
February 5, 2004

SEAN McGARRY
PRIMARY EXAMINER
1635